where the lipophilic liquid vehicle and the solid particles of the camptothecin are positioned within the outer layer of the given droplet;

wherein upon thermal sterilization the dispersion does not aggregate, flocculate, agglomerate, or coalesce, and the droplets do not grow in size above a volume weighted mean diameter of 10 μm.

19. (Amended) An injectable pharmaceutical composition comprising:

an aqueous carrier solution comprising one or more pharmaceutically acceptable tonicity modifier agents;

a dispersion of liquid droplets having a size range of submicrometer to micrometers, the liquid droplets comprising

at least one membrane-forming amphipathic lipid that forms an outer layer of a given droplet,

a substantially water-insoluble, pharmaceutically acceptable lipophilic liquid vehicle, and

solid particles of 9-nitro-20(S)-camptothecin,

where the lipophilic liquid vehicle and the solid particles of the camptothecin are positioned within the outer layer of the given droplet;

wherein upon thermal sterilization, the dispersion does not aggregate, flocculate, agglomerate, or coalesce, and the droplets do not grow in size above a volume weighted mean diameter of 10 μm.

REMARKS

This Amendment is in response to the Examiner's Office Action dated December 18, 2001. Reconsideration is respectfully requested in view of the above amendments and the following remarks.

1. Rejection Under 35 USC 112, Second Paragraph

The Examiner rejects claims 1-30 under 35 USC 112, Second Paragraph for indefiniteness.

The Examiner rejects the independent claims on the grounds that it is confusing whether the phospholipid layer surronds a single droplet or multiple droplet. Independent claims 1, 18 and 19 have been amended to specify that a given droplet has an outer layer comprising a membrane-forming amphipathic lipid as well as what is comprised within the outer layer. Withdrawal of this ground of rejection is requested in view of the amendments to the independent claims.

The Examiner also rejects independent claim 19 for indefiniteness. Applicants submit that the claim as amended is definite and request withdrawal of this ground of rejection.

The Examiner also rejects claims 22 and 23 for their use of Lipoid. After diligent investigation, Applicants where unable to identify a chemical name for this product. Accordingly, use of this language in the claims in the absense of an alternative is appropriate.

2. **Rejection Under 35 USC 103**

The Examiner rejects claims 1-8 and 12-17 under 35 USC 103 as being rendered obvious by U.S. Patent No. 4,725,442 alone or in combination with U.S. Patent No. 5,552,156.

The Examiner also rejects claims 1-9 and 18-30 under 35 USC 103 as being rendered obvious by U.S. Patent No. 4,725,442 alone or in combination with U.S. Patent No. 5,552,156 in further view of WO 99/61001.

The Examiner's attention is drawn to page 54, line 35 – page 56, line 15. As explained in this section of the Specification, the claimed camptothecin formulations were shown to have surprisingly superior efficacy than other drugs (CAMPTOSTAR, HYCAMTIN, DTIC) and 9-nitro-20(S)-camptothecin in DMA. The claimed formulations also have roughly comparable efficacy as oral 9-nitro-20(S)-camptothecin. Such results are quite surprising and unexpected. Given that there is no teaching in the art that the claimed formulations would be highly effective in combination with camptothecins, Applicants' decision to combine the claimed formulation with camptothecins is inventive and rebuts the Examiner's prima *facie case* for obviousness. Allowance of the pending claims is therefore respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

CONCLUSION

In light of the Amendments and the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Date: April 10, 2002

By: David J. Weitz

David J. Weitz
Registration No. 38,362

650 Page Mill Road
Palo Alto, California 94304
(650) 493-9300

VERSION WITH MARKINGS SHOWING CHANGES MADE

Claims 1, 18 and 19 have been amended as follows:

1. (Amended) An injectable pharmaceutical composition comprising:

an aqueous suspension of microdroplets suitable for intravenous delivery, the microdroplets having a mean diameter between 200 Angstroms and one micron, the microdroplets comprising a substantially water-insoluble, pharmacologically acceptable liquid, [a camptothecin] 9-nitro-20(S)-camptothecin dissolved in the water-insoluble, and pharmacologically acceptable liquid [, and] that are positioned within an outer layer of the microdroplet that [comprising] comprises a phospholipid.

18. (Amended) An injectable pharmaceutical composition comprising:

a dispersion in an aqueous carrier solution comprising one or more pharmaceutically acceptable tonicity modifier agents and liquid droplets having a size range of micrometer to submicrometer, the droplets comprising

at least one membrane-forming amphipathic lipid that forms an outer layer of a given droplet,

a substantially water-insoluble, pharmaceutically acceptable lipophilic liquid vehicle, and

[a camptothecin] 9-nitro-20(S)-camptothecin.dissolved in the lipophilic liquid vehicle, [and]

[an outer layer surrounding the droplet comprising at least one membrane-forming amphipathic lipid,]

where the lipophilic liquid vehicle and the solid particles of the camptothecin are positioned within the outer layer of the given droplet;

wherein upon thermal sterilization the dispersion does not aggregate, flocculate, agglomerate, or coalesce, and the droplets do not grow in size above a volume weighted mean diameter of 10 μm.

19. (Amended) An injectable pharmaceutical composition comprising:

an aqueous carrier solution comprising one or more pharmaceutically acceptable tonicity modifier agents;

a dispersion of liquid droplets [of a first size distribution] having a size range of submicrometer to micrometers, the liquid droplets comprising

at least one membrane-forming amphipathic lipid that forms an outer layer of a given droplet,

a substantially water-insoluble, pharmaceutically acceptable lipophilic liquid vehicle, and

solid particles of [a camptothecin] 9-nitro-20(S)-camptothecin, [of a second size distribution, and]

[an outer layer surrounding the droplet comprising at least one membrane-forming amphipathic lipid] where the lipophilic liquid vehicle and the solid particles of the camptothecin are positioned within the outer layer of the given droplet;

[wherein the first size distribution is in the range of submicrometer to micrometers, and the second size distribution is smaller than the first size distribution; and]

wherein upon thermal sterilization, the dispersion does not aggregate, flocculate, agglomerate, or coalesce, and the droplets do not grow in size above a volume weighted mean diameter of 10 μm.